CLAIMS

What is claimed is:

1. A method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject who has, or is a candidate for, atrial fibrillation, comprising administering to the subject an amount of JTV-519 effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject, wherein the RyR2 is atrial RyR2.

2. The method of claim 1, wherein the decrease in the level of RyR2-bound FKBP12.6 is limited or prevented in the subject by decreasing the level of phosphorylated RyR2 in the subject.

3. The method of claim 1, wherein the subject is a human.

4. The method of claim 1, wherein the amount of JTV-519 effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject is an amount of JTV-519 effective to treat or prevent atrial fibrillation in the subject.

5. The method of claim 1, wherein the JTV-519 treats or prevents atrial fibrillation in the subject.

6. The method of claim 1, wherein the amount of JTV-519 effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject is from about 5 mg/kg/day to about 20 mg/kg/day.

7. Use of JTV-519 in a method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject who has, or is a candidate for, atrial fibrillation.

8. A method for treating or preventing atrial fibrillation in a subject, comprising administering to the subject an amount of JTV-519 effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject, thereby treating or preventing atrial fibrillation in the subject.

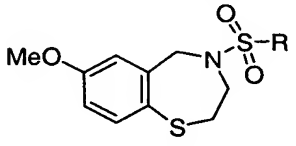
9. The method of claim 8, wherein the atrial fibrillation is non-sustained atrial fibrillation.

10. The method of claim 8, wherein the amount of JTV-519 effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject is an amount of JTV-519 effective to treat or prevent atrial fibrillation in the subject.

11. The method of claim 10, wherein the JTV-519 treats or prevents atrial fibrillation in the subject.

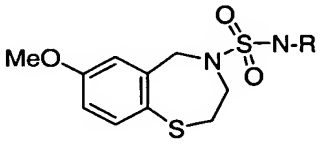
12. The method of claim 8, wherein the amount of JTV-519 effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject is from about 5 mg/kg/day to about 20 mg/kg/day.

13. A method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject, comprising administering an agent to the subject, in an amount effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject, wherein the agent is selected from the group consisting of:



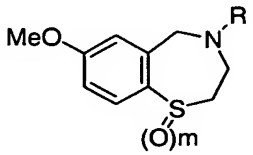
(a)

wherein R = aryl, alkenyl, alkyl, -$(CH_2)_nNR'_2$, or -$(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



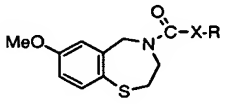
(b)

wherein R = aryl, alkyl, -$(CH_2)_nNR'_2$, or -$(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



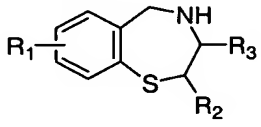
(c)

wherein R = $CO(CH_2)_nXR'_2$, $SO_2(CH_2)_nXR'_2$, or $SO_2NH(CH_2)_nXR'_2$, and X = N or S, and n = 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein m = 1 or 2;



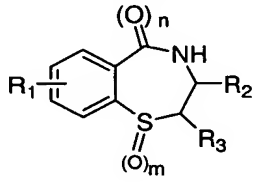
(d)

wherein R = aryl, alkyl, $-(CH_2)_nNR'_2$, $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein X = NH or O;



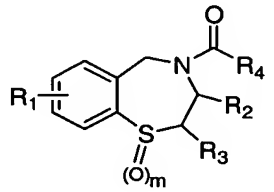
(e)

wherein R_1 = OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or H; wherein R_2 = H, alkyl, or aryl; and wherein R_3 = H, alkyl, or aryl;



(f)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein m = 0, 1, or 2; and wherein n = 0 or 1;



(g)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein R4 = H, halide, alkenyl, carboxylic acid, or an alkyl containing O, S, or N; and wherein m = 0, 1, or 2; and

(h) any oxidized form thereof.

14. The method of claim 13, wherein the decrease in the level of RyR2-bound FKBP12.6 is limited or prevented in the subject by decreasing the level of phosphorylated RyR2 in the subject.

15. The method of claim 13, wherein the subject is a human.

16. The method of claim 13, wherein the subject has catecholaminergic polymorphic ventricular tachycardia (CPVT).

17. The method of claim 13, wherein the subject has, or is a candidate for, a cardiac arrhythmia, heart failure, and/or exercise-induced sudden cardiac death.

18. The method of claim 13, wherein the amount of the agent effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject is an amount of the agent effective to treat or prevent a cardiac arrhythmia, heart failure, and/or exercise-induced sudden cardiac death in the subject.

19. The method of claim 18, wherein the cardiac arrhythmia is an atrial arrhythmia or a ventricular arrhythmia.

20. The method of claim 19, wherein the atrial arrhythmia is atrial fibrillation.

21. The method of claim 21, wherein the atrial fibrillation is sustained atrial fibrillation.

22. The method of claim 19, wherein the ventricular arrhythmia is exercise-induced ventricular arrhythmia.

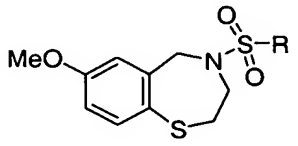
23. The method of claim 13, wherein the agent treats or prevents a cardiac arrhythmia, heart failure, and/or exercise-induced sudden cardiac death in the subject.

24. The method of claim 13, wherein the amount of agent effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject is from about 5 mg/kg/day to about 20 mg/kg/day.

25. The method of claim 13, wherein the agent is S4, S7, S-20, S-24, S-25, S-26, S-27, or S36.

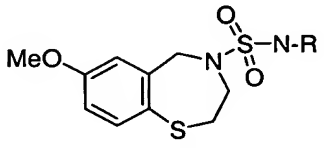
26. The method of claim 25, wherein the agent is S36.

27. Use of an agent in a method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject, wherein the agent is selected from the group consisting of:



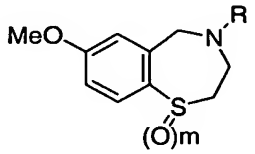
(a)

wherein R = aryl, alkenyl, alkyl, -$(CH_2)_nNR'_2$, or -$(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



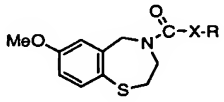
(b)

wherein R = aryl, alkyl, -$(CH_2)_nNR'_2$, or -$(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



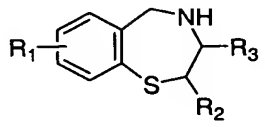
(c)

wherein R = $CO(CH_2)_nXR'_2$, $SO_2(CH_2)_nXR'_2$, or $SO_2NH(CH_2)_nXR'_2$, and X = N or S, and n = 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein m = 1 or 2;



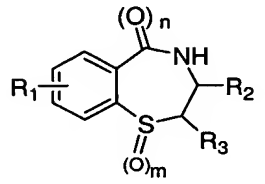
(d)

wherein R = aryl, alkyl, $-(CH_2)_nNR'_2$, $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein X = NH or O;



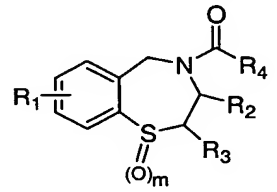
(e)

wherein R_1 = OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or H; wherein R_2 = H, alkyl, or aryl; and wherein R_3 = H, alkyl, or aryl;



(f)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein m = 0, 1, or 2; and wherein n = 0 or 1;

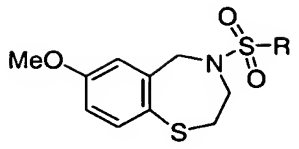


(g)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein R4 = H, halide, alkenyl, carboxylic acid, or an alkyl containing O, S, or N; and wherein m = 0, 1, or 2; and

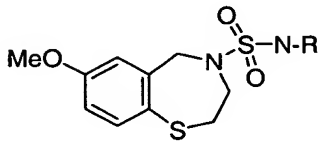
(h) any oxidized form thereof.

28. A method for treating or preventing a cardiac arrhythmia, heart failure, and/or exercise-induced sudden cardiac death in a subject, comprising administering an agent to the subject, in an amount effective to limit or prevent a decrease in the level of RyR2-bound FKBP12.6 in the subject, wherein the agent is selected from the group consisting of:



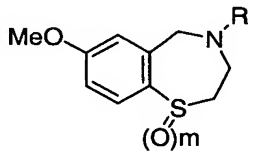
(a)

wherein R = aryl, alkenyl, alkyl, $-(CH_2)_nNR'_2$, or $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



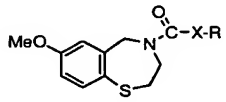
(b)

wherein R = aryl, alkyl, $-(CH_2)_nNR'_2$, or $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



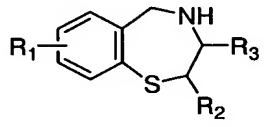
(c)

wherein R = $CO(CH_2)_nXR'_2$, $SO_2(CH_2)_nXR'_2$, or $SO_2NH(CH_2)_nXR'_2$, and X = N or S, and n = 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein m = 1 or 2;



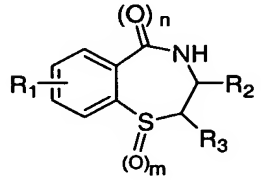
(d)

wherein R = aryl, alkyl, $-(CH_2)_nNR'_2$, $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein X = NH or O;



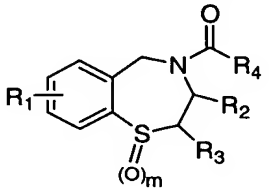
(e)

wherein R_1 = OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or H; wherein R_2 = H, alkyl, or aryl; and wherein R_3 = H, alkyl, or aryl;



(f)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein m = 0, 1, or 2; and wherein n = 0 or 1;

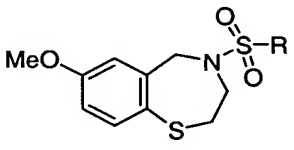


(g)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein R4 = H, halide, alkenyl, carboxylic acid, or an alkyl containing O, S, or N; and wherein m = 0, 1, or 2; and

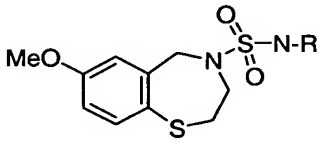
(h) any oxidized form thereof.

29. A method for treating or preventing a cardiac arrhythmia, heart failure, and/or exercise-induced sudden cardiac death in a subject, comprising administering an agent to the subject, in an amount effective to treat or prevent the cardiac arrhythmia, heart failure, and/or exercise-induced sudden cardiac death in the subject, wherein the agent is selected from the group consisting of:



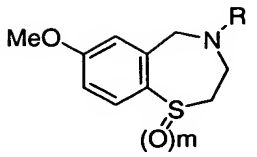
(a)

wherein R = aryl, alkenyl, alkyl, $-(CH_2)_nNR'_2$, or $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



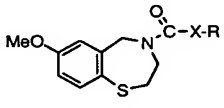
(b)

wherein R = aryl, alkyl, $-(CH_2)_nNR'_2$, or $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



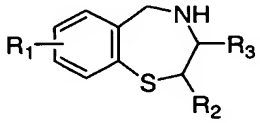
(c)

wherein R = $CO(CH_2)_nXR'_2$, $SO_2(CH_2)_nXR'_2$, or $SO_2NH(CH_2)_nXR'_2$, and X = N or S, and n = 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein m = 1 or 2;



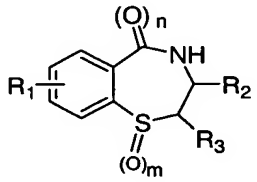
(d)

wherein R = aryl, alkyl, $-(CH_2)_nNR'_2$, $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein X = NH or O;



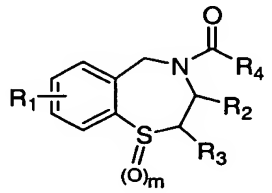
(e)

wherein R_1 = OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or H; wherein R_2 = H, alkyl, or aryl; and wherein R_3 = H, alkyl, or aryl;



(f)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein m = 0, 1, or 2; and wherein n = 0 or 1;



(g)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl,

alkenyl, or aryl; wherein R4 = H, halide, alkenyl, carboxylic acid, or an alkyl containing O, S, or N; and wherein m = 0, 1, or 2; and

(h) any oxidized form thereof.

30. The method of claim 29, wherein the cardiac arrhythmia is an atrial arrhythmia or a ventricular arrhythmia.

31. The method of claim 30, wherein the atrial arrhythmia is atrial fibrillation.

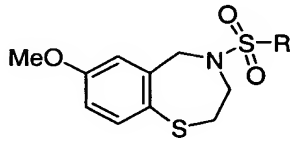
32. The method of claim 30, wherein the ventricular arrhythmia is exercise-induced ventricular arrhythmia.

33. The method of claim 29, wherein the amount of agent effective to treat or prevent a cardiac arrhythmia, heart failure, and/or exercise-induced sudden cardiac death in the subject is from about 5 mg/kg/day to about 20 mg/kg/day.

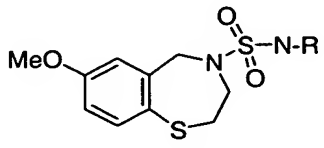
34. The method of claim 29, wherein the agent is S4, S7, S-20, S-24, S-25, S-26, S-27, or S36.

35. The method of claim 34, wherein the agent is S36.

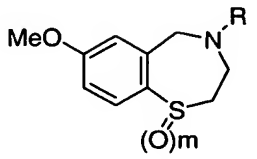
36. Use of an agent in a method for treating or preventing a cardiac arrhythmia, heart failure, and/or exercise-induced sudden cardiac death in a subject, wherein the agent is selected from the group consisting of:

(a) 

wherein R = aryl, alkenyl, alkyl, $-(CH_2)_nNR'_2$, or $-(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;

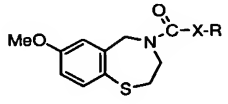
(b) 

wherein R = aryl, alkyl, -$(CH_2)_nNR'_2$, or -$(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl;



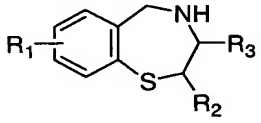
(c)

wherein R = $CO(CH_2)_nXR'_2$, $SO_2(CH_2)_nXR'_2$, or $SO_2NH(CH_2)_nXR'_2$, and X = N or S, and n = 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein m = 1 or 2;



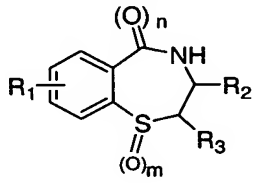
(d)

wherein R = aryl, alkyl, -$(CH_2)_nNR'_2$, -$(CH_2)_nSR'$, and n = 0, 1, 2, or 3, and R' = alkyl or cycloalkyl; and wherein X = NH or O;



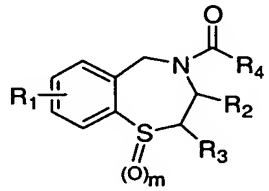
(e)

wherein R_1 = OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or H; wherein R_2 = H, alkyl, or aryl; and wherein R_3 = H, alkyl, or aryl;



(f)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein m = 0, 1, or 2; and wherein n = 0 or 1;



(g)

wherein R1 = H, OR', SR', NR', alkyl, or halide, at position 2, 3, 4, or 5 on the phenyl ring, and R' = alkyl, aryl, or acyl; wherein R2 = H, alkyl, alkenyl, or aryl; wherein R3 = H, alkyl, alkenyl, or aryl; wherein R4 = H, halide, alkenyl, carboxylic acid, or an alkyl containing O, S, or N; and wherein m = 0, 1, or 2; and

(h) any oxidized form thereof.

37. A method for identifying an agent for use in treating or preventing atrial fibrillation or heart failure, comprising the steps of:

(a) obtaining or generating a culture of cells containing RyR2;

(b) contacting the cells with a candidate agent;

(c) exposing the cells to one or more conditions known to increase phosphorylation of RyR2 in cells; and

(d) determining if the agent limits or prevents a decrease in the level of RyR2-bound FKBP12.6 in the cells.

38. The method of claim 37, further comprising the step of:

(e) determining if the agent has an effect on an RyR2-associated biological event in the cells.

39. An agent identified by the method of claim 37.

40. A method for identifying an agent for use in treating or preventing atrial fibrillation or heart failure, comprising the steps of:

(a) obtaining or generating an animal containing RyR2;

(b) administering a candidate agent to the animal;

(c) exposing the animal to one or more conditions known to increase phosphorylation of RyR2 in cells; and

(d) determining if the agent limits or prevents a decrease in the level of RyR2-bound FKBP12.6 in the animal.

41. The method of claim 40, further comprising the step of:

(e) determining if the agent has an effect on an RyR2-associated biological event in the animal.

42. An agent identified by the method of claim 40.